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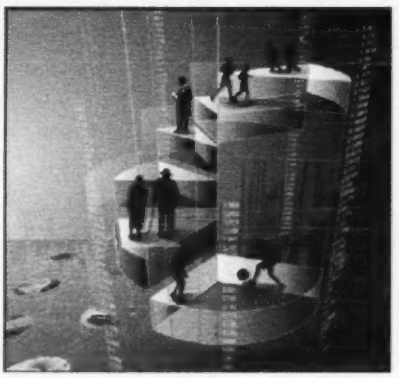
Clinical outcomes of modelling mammography screening strategies



by Martin J. Yaffe, Nicole Mittmann, Pablo Lee, Anna N.A. Tosteson, Amy Trentham-Dietz, Oguzhan Alagoz and Natasha K. Stout

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...	not applicable
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^{p}	preliminary
^{r}	revised
x	suppressed to meet the confidentiality requirements of the *Statistics Act*
^{E}	use with caution
F	too unreliable to be published
*	significantly different from reference category ($p < 0.05$)

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Clinical outcomes of modelling mammography screening strategies

by Martin J. Yaffe, Nicole Mittmann, Pablo Lee, Anna N.A. Tosteson, Amy Trentham-Dietz, Oguzhan Alagoz and Natasha K. Stout

Abstract

Background: A validated breast cancer model can be used to compare health outcomes associated with different screening strategies.

Data and methods: The University of Wisconsin Cancer Intervention and Surveillance Modeling Network (CISNET) breast cancer microsimulation model was adapted to simulate breast cancer incidence, screening performance and delivery of optimal therapies in Canada. The model considered effects of breast density on incidence and screening performance. Model predictions of incidence, mortality and life-years (LY) gained for a 1960 birth cohort of women for No Screening were compared with 11 digital mammography screening strategies that varied by starting and stopping age and frequency.

Results: In the absence of screening, the estimate of LYs lost from breast cancer was 360.1 per 1,000 women, and each woman diagnosed with breast cancer after age 40 who dies of breast cancer would lose an estimated average of 19.1 years. Biennial screening at ages 50 to 74 resulted in an estimated 116.3 LYs saved. Annual screening at ages 40 to 49, followed by biennial screening to age 74, resulted in an estimated 170.3 LY saved. That is, adding annual screening at ages 40 to 49 saved an additional 54 LY per 1,000 women. Screening annually at ages 40 to 74 recovered the most: 214 LY saved. More frequent screening was associated with an increased ratio of detection of ductal *in situ* to invasive cancers, more abnormal recalls and more negative biopsies, but a reduction in the number of women required to be screened per life saved or per LY saved.

Interpretation: In general, mortality reduction was found to be associated with the total number of lifetime screens for breast cancer. However, for the same number of screens, more frequent screening after age 50 appeared to have a greater impact on breast cancer deaths averted than did beginning screening earlier. When the number of LYs saved by screening was considered, a greater impact was achieved by screening women in their 40s than by reducing the interval between screens.

Key words: Breast screening, health outcomes, microsimulation model, preventive health

Organized provincial breast cancer screening programs in Canada typically include: a mechanism to invite eligible women to attend at recommended intervals, standardized reporting, quality assurance, monitoring of outcomes, and a link between the screening process and subsequent imaging to assess suspicious findings. However, the age range and frequency of population screening have been subjects of debate, and implementation of screening varies across the country.

This analysis employs a validated microsimulation model of breast cancer, adapted to the Canadian context,[1] to predict health outcomes associated with different digital mammography screening strategies (including No Screening) across different age ranges. The model estimates the benefits, harms, limitations, and use of resources for each strategy.

Methods

Model

A computer simulation modelling approach was used to examine the health benefits and costs of digital mammography for 11 screening strategies, which vary by age of starting and ceasing screening and frequency of examinations, compared with No Screening (Text table 1). They represent screening strategies used in various Canadian jurisdictions and recommendations of the U.S. Preventive Services Task Force[2,3] and the Canadian Task Force on Preventive Health Care.[4] Because of interest in the impact of screening at ages 40 to 49, annual screening of this age group was also modelled.

The health outcomes are breast cancer mortality reduction and life-years (LY) saved, compared with No Screening. Expected resource use (number of mammograms, diagnostic work-up of positive findings from screening, therapeutic procedures, and management per screening strategy) was also modelled.

The model[5,6] has been used to study the efficacy and cost-effectiveness of breast cancer screening.[7-9] Its adaptation to the Canadian context is described in a companion paper.[1] The framework for the outcome analysis is the University of Wisconsin Breast Cancer Epidemiology Simulation Model, developed under the U.S. National Cancer Institute-funded Cancer Intervention and Surveillance Modeling Network (CISNET) program. The model was Canadianized under a grant provided by The Canadian Breast Cancer Foundation.

For each screening strategy, the model predicted age-specific incidence and mortality. Based on life tables, the number of LY lost to breast cancer detected at each age was estimated.[10]

The calculations pertain to a single birth cohort—women born in 1960. This allows estimation of age-specific breast cancer outcomes, such as incidence and mortality, independent of cross-sectional population-based effects associated with year

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Text table 1
Digital mammography screening strategies modelled

No Screening
Annual 40 to 69
Annual 40 to 74
Annual 50 to 69
Annual 50 to 74
Biennial 40 to 74
Biennial 50 to 69
Biennial 50 to 74
Triennial 50 to 69
Triennial 50 to 74
Annual 40 to 49, Biennial 50 to 69
Annual 40 to 49, Biennial 50 to 74

Source: Canadianized University of Wisconsin Breast Cancer Epidemiology Simulation Model.

of birth. Published data were used to describe the accuracy of cancer detection and the efficacy of treatment in the model.[9,11]

Clinical input parameters

Upon tumour detection, all women received baseline treatment (for example, surgery with or without radiation). Adjuvant treatment was assigned based on age, breast cancer stage, and hormone receptor status.

The percentages of women with ER+/ER- (estrogen receptor positive/estrogen receptor negative) disease were assigned by the model, based on U.S. SEER data.[12,13] Assignment of HER2 (human epidermal growth factor receptor 2) status was added.[14]

Treatment effectiveness was implemented by a "cure"/"no cure" model. A woman who is "cured" will not die of breast cancer; a woman who is not "cured" may die of breast cancer or non-breast cancer causes. Baseline cure fractions by stage at detection were determined by model calibrations. These baseline cure fractions were modified by the presence of adjuvant treatment using observed hazard reductions from clinical trials (Text table 2).[11]

Outcome measures

For each woman, the model recorded age at detection of a breast cancer, its "stage" (*in situ*, local invasive, regional involvement, or distant metastasis), age at which she died, and whether the death was attributable to breast cancer or another cause. Calculations were made for a birth cohort of 2,000,000 women for each screening strategy. Results are expressed as age- and stage-specific incidence and mortality per 1,000 women in the cohort who were alive at age 40 (abbreviated to "per 1,000"). Mortality reductions attributable to screening were obtained by comparing the number of deaths due to breast cancer for each screening strategy with the corresponding number for No Screening at ages 40 to 99. The number of recalls following screening without a finding of cancer and the number of biopsies that were negative were calculated, as well as the number of screening examinations and the number of women required to be screened per life saved and per LY saved.

To estimate the number of LYs lost to breast cancer, the age at which a woman died because of breast cancer as predicted by the model was compared with the mean age at which she would be expected to die based on Canadian life tables.[10]

Results

The model predicts that with No Screening, in a 1960 birth cohort of 2,000,000 women, 37,075 (1.9% of the cohort or 12% of those who developed breast cancer) would die of breast cancer, and 259,342 (13% of the cohort or 87% of those who developed breast cancer) would die of other causes (data not shown). On average, each woman diagnosed with breast cancer after age 40 who died of breast cancer lost 19.1 LYs. In the absence of screening, the number of LYs lost to breast cancer per 1,000 women alive at age 40 was 360.

The stage-specific incidence rates of breast cancer provided by the model for No Screening can be compared with the incidence rates for annual screening at ages 50 to 74 (Figure 1). Figure 2 shows deaths due to breast cancer per 100,000, by age, for No Screening, biennial screening at ages 50 to 74, and annual screening at ages 40 to 49 followed by biennial screening until age 74. The effect of screening on mortality reduction persists for some time after the age when screening ceases, but mortality eventually rises toward the unscreened rate.

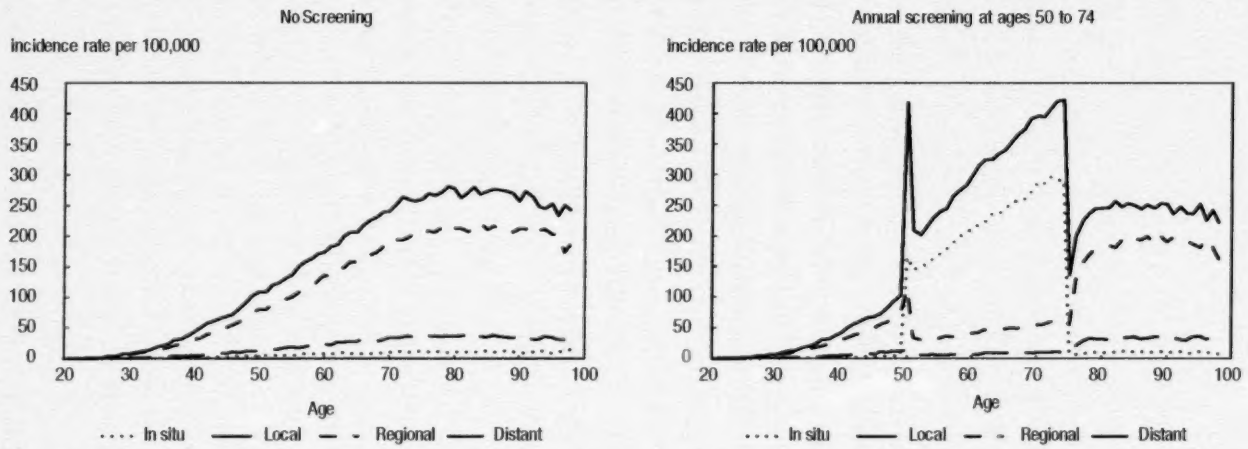
For each screening strategy, Table 1 reports mortality reductions based on deaths that occurred between the age

Text table 2
Mortality reduction associated with adjuvant treatment, by receptor status, age range, and breast cancer stage

		Mortality reduction, % (treatment type)	
Receptor status	**Age**	**Ductal carcinoma *in situ***	**Invasive cancer, including distant**
ER +	Younger than 50	32 (tamoxifen)	58 (chemotherapy and tamoxifen)
	50 or older	32 (tamoxifen)	53 (chemotherapy and aromatase inhibitor)
ER -	Younger than 50	0 (no adjuvant)	38 (chemotherapy)
	50 or older	0 (no adjuvant)	38 (chemotherapy)
HER2+	All ages	0 (no adjuvant)	33 (herceptin)

ER+/ER- = estrogen receptor positive/estrogen receptor negative
HER2 = human epidermal growth factor receptor 2
Source: Early Breast Cancer Trialists' Collaborative Group (EBCTCG).[11]

Figure 1
Age-specific breast cancer incidence rate per 100,000, by stage, for No Screening and annual screening at ages 50 to 74



Source: Canadianized University of Wisconsin Breast Cancer Epidemiology Simulation Model.

when screening began and 15 years after screening was discontinued. This more realistically shows the effect when screening ceases many years before life expectancy. It also emulates calculations that would be done in a randomized trial with a finite follow-up period, in this case 15 years after the screening intervention.

Table 1 also summarizes the outcomes of each strategy, with a focus on efficiency. The maximum number of screening examinations that a woman could receive during her lifetime is given for each strategy, along with the number of screening examinations that must be conducted per breast cancer death averted, and the number of women who must be screened per death averted and per LY gained.

In general, the extent of mortality reduction was associated with the total number of lifetime screens (Figure 3). However, in terms of breast cancer deaths averted, for the same number of screens, more frequent screening after age 50 appears to have a greater impact than beginning screening earlier.

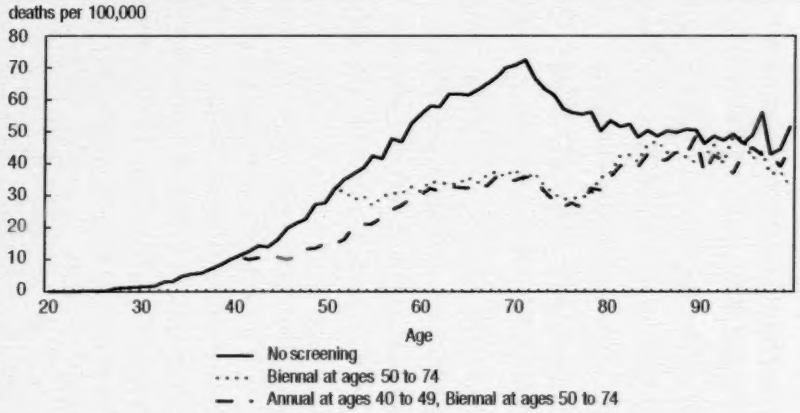
When the number of LYs saved is considered, the story changes—a greater impact was achieved by screening women in their 40s than by reducing the interval between screens (Figure 4). The model also predicts that outcomes for the hybrid

Table 1
Breast cancer deaths averted, mortality reduction, life-years (LY) saved, screening examinations per woman, women needed to be screened per death averted, and women needed to be screened per LY gained, compared with No Screening, by screening strategy

Screening strategy	Breast cancer deaths averted per 1,000 women alive at age 40	Mortality reduction (%) with 15 years follow-up	LY saved per 1,000 women alive at age 40	Maximum screening examinations per woman	Screening examinations per death averted	Women screened per death averted	Women screened per LY gained
Annual 40 to 69	9.1	50.2	201.1	30	2,984	99	4.5
Annual 40 to 74	10.1	53.4	213.5	35	3,023	86	4.1
Annual 50 to 69	7.4	45.5	148.0	20	2,360	118	5.9
Annual 50 to 74	8.4	49.2	160.9	25	2,484	99	5.2
Biennial 40 to 74	7.3	38.5	149.8	18	2,165	138	6.7
Biennial 50 to 69	5.2	32.3	105.2	10	1,696	170	8.4
Biennial 50 to 74	6.1	35.9	116.3	13	1,783	137	7.2
Triennial 50 to 69	4.0	24.6	80.0	7	1,557	222	11.1
Triennial 50 to 74	4.8	27.9	89.2	9	1,589	177	9.4
Annual 40 to 49, Biennial 50 to 69	7.0	38.7	158.2	20	2,651	133	5.9
Annual 40 to 49, Biennial 50 to 74	7.9	42.0	170.3	22	2,593	118	5.5
Annual 40 to 49	2.0	18.6	58.0	10	5,152	526	17.2

Source: Canadianized University of Wisconsin Breast Cancer Epidemiology Simulation Model.

Figure 2
Age-specific mortality rate per 100,000 for No Screening, biennial screening at ages 50 to 74, and annual screening at ages 40 to 49 followed by biennial screening at ages 50 to 74



Source: Canadianized University of Wisconsin Breast Cancer Epidemiology Simulation Model.

strategies, in which the screening interval is lengthened from annual to biennial at an age approximating menopause (in this case, 50), were superior to those for biennial or triennial screening, but not as good as those for annual screening.

Table 2 presents the number of screening examinations for each strategy, recalls for non-invasive imaging whose outcome is negative (no cancer), and negative breast biopsies arising from the lifetime screening experience for each strategy per 1,000 women alive at age 40. Greater intensity or longer duration of screening increased the probability that a woman would be recalled for further imaging that turned out to be negative, and the probability of undergoing a biopsy that was negative for breast cancer. These biopsies are performed after both a suspicious (positive) screening result and a positive result of additional non-invasive imaging have occurred. The calculation incorporated British Columbia data on the positive yield of biopsies[15]: 16.6% for women in their 40s; 33.7% for those in their 50s; 49.2% for those in their 60s; and 54.7% for those in their 70s. Based on these data, from the number of cancers detected, the number of biopsies that would be performed on women who did not have breast cancer was estimated. The numbers were lowest for biennial and triennial screening at ages 50 to 69 (144 and 141 per 1,000, respectively) and highest for annual screening at ages 40 to 74 (308 per 1,000).

Table 2
Number of screening examinations, number of recalls for non-invasive imaging and no cancer found, and number of negative biopsies, per 1,000 women alive at age 40, by screening strategy

Screening strategy	Screening examinations	Recalled for no cancer		Negative biopsies	
		Number	%	Number	%
Annual 40 to 69	27,064	2,623	9.7	276	1.0
Annual 40 to 74	30,439	2,865	9.4	308	1.0
Annual 50 to 69	17,405	1,528	8.8	163	0.9
Annual 50 to 74	20,805	1,773	8.5	195	0.9
Biennial 40 to 74	15,741	1,698	10.8	276	1.8
Biennial 50 to 69	8,817	895	10.2	144	1.6
Biennial 50 to 74	10,887	1,069	9.8	179	1.6
Triennial 50 to 69	6,188	699	11.3	141	2.3
Triennial 50 to 74	7,561	826	10.9	173	2.3
Annual 40 to 49, Biennial 50 to 69	18,537	1,906	10.3	258	1.4
Annual 40 to 49, Biennial 50 to 74	20,592	2,052	10.0	292	1.4

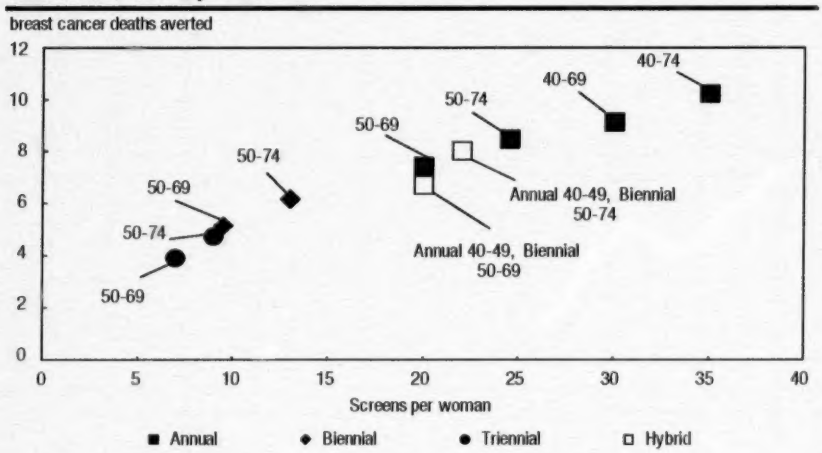
Source: Canadianized University of Wisconsin Breast Cancer Epidemiology Simulation Model.

Discussion

As expected, in the absence of screening (Figure 1), the observed incidence of *in situ* cancer is very low, with most cancers being detected by the woman herself or clinically when they are invasive and either local or regional (nodal metastases). A comparison of the No Screening predictions with those for screening—in this case, annual at ages 50 to 74—shows that screening results in a downward stage shift, with more *in situ* and localized invasive cancers detected and less disease discovered at more advanced stages during the period when screening is performed. Incidence returns to the non-screened level fairly rapidly when screening is discontinued, at age 74 in this example.

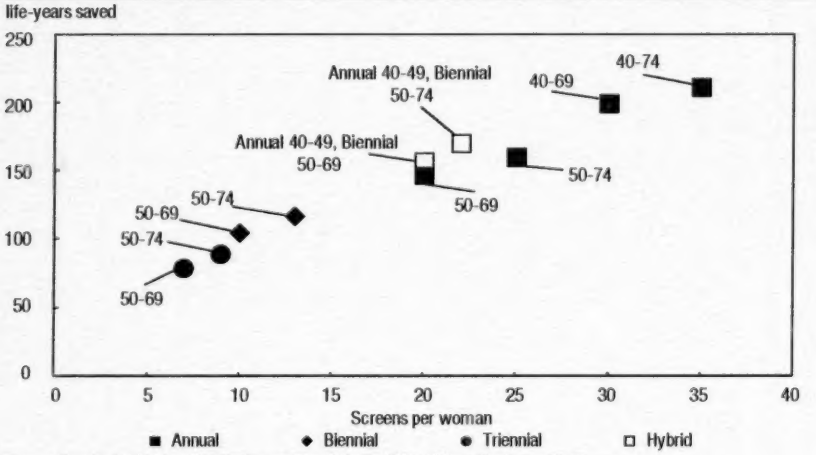
On the initial screen at age 40 or 50, a "spike" in breast cancer detection is evident. These "prevalent" cancers, which were occult in previous years when screening did not occur, will include a number that are larger and more advanced than those detected on subsequent screens. Some may be slow-growing cancers that are unlikely to be lethal, but others will be lethal and represent the potential for reducing mortality had they been detected earlier by screening. This possibility is supported by the model. For annual screening beginning at age 40, the model predicts that 11.2% of the women with prevalent invasive cancers, detected at age 40, will die of breast cancer. This is similar to the

Figure 3
Breast cancer deaths averted per 1,000 women alive at age 40, by number of lifetime screens per woman



Source: Canadianized University of Wisconsin Breast Cancer Epidemiology Simulation Model.

Figure 4
Life-years saved (undiscounted) per 1,000 women alive at age 40, by number of lifetime screens per woman



Source: Canadianized University of Wisconsin Breast Cancer Epidemiology Simulation Model.

value of 9.4% for women whose cancers were detected in the next screen at age 41—that is, mortality due to prevalent cancers is about the same as that associated with incident cancers. Similarly, if screening starts at age 50, 10.9% of those with breast cancers detected in the prevalence screen at age 50 will die of breast cancer, and 8.3% of those with incident cancers detected in the next screen at age 51 will die.

For screening that begins around age 40, the model shows a reduction of mortality for all strategies compared with No Screening, with the reduction starting about two years after the initiation of screening (Figure 2). The sharp drop in mortality suggests advantage in earlier detection, even for more advanced cancers. This can be inferred from the model, in that the natural history of the cancers in the screened and unscreened cohorts is the same until the point when screening begins. Treatment of some of the cancers detected on the first screen results in some women being alive two years later, while their counterparts in the unscreened cohort have died. Given the very high survival for early-stage breast cancer, this implies that the cancers in both groups must have been fairly advanced to produce such a pronounced effect at two years. The mortality reduction diminishes shortly after screening ceases, becoming minimal around age 89, 15 years after screening has ended.

A strategy that has been suggested is to screen annually at ages 40 to 49 (or slightly older), and then biennially until age 74. When this strategy is compared with biennial screening at ages 50 to 74 (now operational in several provinces), the model predicts 1.8 fewer breast-cancer-related deaths and 54 LYs saved per 1,000 women alive at age 40. Given that approximately 230,000 women in Canada turn 40 each year, annual screening at ages 40 to 49 translates into approximately 414 premature deaths averted and 12,420 LYs saved each year.

For the same cohort and the two screening strategies, multiplying differences in values in Table 2 by the same factor (230) predicts that a total of 2,232,150 additional screening examinations would be performed over the cohort's collective lifetime. There would be 226,090 additional recalls for further imaging examinations where cancer was not found and 25,990 negative biopsies. However, Table 2 slightly underestimates the specificity achieved in Canadian screening, which is closer to 93%. If this were the case, the number of additional recalls with no cancer found would decrease to 210,060, and the number of additional negative biopsies, to 24,170. Both of these factors scale directly with (1-Sp), and therefore, even small improvements in specificity would yield substantial reductions in recall examinations and negative biopsies. For this reason, digital breast tomosynthesis has attracted considerable interest as a possible replacement for mammography, as early studies have shown up to a 30% improvement in Sp.[16]

What is already known on this subject?

- In Canada, the age range and frequency of population digital mammography screening have been subjects of debate, and implementation of screening varies across the country.
- The University of Wisconsin Breast Cancer Epidemiology Simulation Model can compare outcomes of population-level digital mammography screening strategies.
- This model was adapted to the Canadian context.

What does this study add?

- More frequent screening and beginning at age 40 detected more breast cancers, and at earlier stages.
- More frequent screening and beginning at age 40 resulted in fewer deaths and fewer life-years lost, but also, more recalls when no breast cancer was found and more negative biopsies.

The model predicts that a much lower number of women would have to be screened to avert a breast cancer death than reported in the U.S. and Canadian Task Force Recommendations.[2,4] For example, for annual screening at ages 40 to 49, the model predicts that 526 women would have to be screened per breast cancer death averted; the Canadian Task Force reported the number as 2,108.[4] This difference occurs, in part, because the Recommendations refer to the number of women *required to be invited* into a randomized trial of screening rather than the number actually *required to be screened* to achieve that benefit.

Strengths and limitations

A strength of this analysis is that the model does not contain explicit assumptions about the mortality reduction provided by screening.

Although all six CISNET models agree in their predictions of cancer incidence and qualitative conclusions about the value of screening and treatment, some variability is evident in the quantitative estimates of benefit associated with screening and treatment. The University of Wisconsin Breast Cancer Simulation model tends to be "optimistic" in terms of the screening benefit,[7,9] but the impact of the difference is not large.

In the model, the growth rate of cancers was not assigned an age dependence, despite some indication that premenopausal cancers grow more quickly.

The analysis assumed full compliance with screening and treatment by all eligible women. To reflect the reality of partial participation, the cohort would simply be split according to the percentage participating in a particular strategy or not receiving screening. The resulting incidence, deaths or LYs lost would be calculated as a weighted combination of the outcomes for the two groups.

Conclusion

According to the model, more frequent screening detected more breast cancers, resulted in fewer breast cancer deaths and years of life lost, and was associated with an increased ratio of *in situ* to invasive cancers detected. At the same time, screening triggers recalls for further imaging examinations where cancer is not found, and also, negative biopsies. The number of negative biopsies was lowest for biennial and triennial screening at ages 50 to 69 and highest for annual screening at ages 40 to 74. ■

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